

REVIEW

Malaria epidemiology and control in refugee camps and complex emergencies

By M. ROWLAND*

HealthNet International, Peshawar, Pakistan, and London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, U.K.

AND F. NOSTEN

Shoklo Malaria Research Unit, Wellcome–Mahidol University–Oxford Tropical Medicine Research Programme, Mae Sot, Thailand

Received 14 February 2001, Revised 3 October 2001,

Accepted 5 October 2001

Owing to the breakdown of health systems, mass population displacements, and resettlement of vulnerable refugees in camps or locations prone to vector breeding, malaria is often a major health problem during war and the aftermath of war. During the initial acute phase of the emergency, before health services become properly established, mortality rates may rise to alarming levels. Establishing good case management and effective malaria prevention are important priorities for international agencies responsible for emergency health services. The operational strategies and control methods used in peacetime must be adapted to emergency conditions, and should be regularly re-assessed as social, political and epidemiological conditions evolve. During the last decade, research on malaria in refugee camps on the Pakistan–Afghanistan and Thailand–Burma borders has led to new methods and strategies for malaria prevention and case management, and these are now being taken up by international health agencies. This experience has shown that integration of research within control programmes is an efficient and dynamic mode of working that can lead to innovation and hopefully sustainable malaria control. United Nations' humanitarian and non-governmental agencies can play a significant part in resolving the outstanding research issues in malaria control.

Over the last quarter of a century, the number of refugees that have fled war and conflict to seek shelter in neighbouring countries has risen from 4.6 million in 1978 to 18.2 million in 1993 (Najera, 1996). A further 24 million individuals were estimated to be internally displaced, often trapped by fighting and inaccessible to international help (Anon., 1995). During the 1970s and 1980s most conflicts occurred in regions that were subject to Cold-

War power struggles (e.g. South–east Asia, Afghanistan, the Horn of Africa and southern Africa). Since the end of the Cold War, civil conflicts have broken out in many countries around the world (e.g. in Tajikistan, Azerbaijan, Sierra Leone, Liberia, Somalia, Burundi, Rwanda and Sudan; Anon., 1997). Countries that host large population displacements rarely have the resources to support them. Responsibility for refugee welfare is shared between the national governments, the United Nations (UN) and non-governmental organizations (NGO). Mortality rates are always highest during the early acute phase of emergencies

* Address for correspondence: London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT, U.K. E-mail: mark.rowland@lshtm.ac.uk; fax: + 44 (0)20 7580 9075.

(Anon., 1997). The priority interventions to reduce death rates in newly established camps are provision of clean water, food, sanitation, shelter, and communicable-disease control (Simmonds *et al.*, 1983; Toole and Waldman, 1990, 1997; Anon., 1997). As security and access to refugees improve during the post-emergency phase, improved health provision becomes feasible. But refugees usually remain vulnerable and assistance may be required until conditions favour a return home, which may take several years in chronic situations (Anon., 1997).

In all the above-named regions or countries, malaria is or was a significant health problem during the emergency, as it is a disease that flourishes in conditions of crisis and population displacement for many reasons: the breakdown of health services and control programmes; the displacement or concentration of non-immune refugees in malaria-risk areas; malnourishment within displaced populations; the siting of camps on marginal land prone to vector breeding; problems in gaining access or supplying medicine to displaced populations; and the lack of protective shelter and other man-vector barriers.

The quality of health service that can be achieved differs between the acute and post-emergency phases. During the acute phase the priority is to prevent deaths and bring disease under control (WHO, 1999). Because clinical diagnosis of malaria is unreliable, microscopy or rapid diagnostic tests must be established as quickly as possible, to improve case management and surveillance (Luxemburger *et al.*, 1998). As malaria transmission is seldom contained by case management alone, preventive measures must also be introduced. The choice of intervention is not prescriptive and will depend on operational conditions, social behaviour, local epidemiology, vector biology, feasibility and cost (WHO, 1999).

There is a paucity of published information on malaria control in complex emergencies. This reflects the difficulty of undertaking the relevant, rigorous or long-term research in changing demographic or unstable political situations. The relevant research on malaria has been mainly confined to long-term refugee

camps situated in comparatively stable, refugee-tolerant countries that border on complex emergencies. The most prominent study sites are those on the borders between Thailand and Burma (Karen refugees) and between Pakistan and Afghanistan (Afghan refugees). Good quality or long-term research is more feasible, or stands more chance of being completed, in the chronic conditions or post-conflict phases that emerge after the acute phase. Sadly, little research has been reported from Africa where most of the malaria burden among refugees occurs. The majority of published accounts of malaria in complex emergencies report on epidemics [in Afghanistan in 1989–1999, Iraq and southern Turkey in 1993–1997, Tajikistan in 1993–1998, Azerbaijan in 1993–1995, Somalia in 1991–1999, Liberia in 1989–1999, and southern Sudan in 1983–1999 (Najera *et al.*, 1998; WHO, 1999)], morbidity or mortality rates (Glass *et al.*, 1980; Shears *et al.*, 1987; Meek, 1988; Lienhardt *et al.*, 1990; Rey *et al.*, 1996; Pitt *et al.*, 1998), the results of surveys of in-vivo drug resistance (Hurwitz *et al.*, 1981; Wolday *et al.*, 1995; Guthman *et al.*, 1996; Rab *et al.*, 2001), or instances of imported malaria (Guerrero *et al.*, 1982; Schultz, 1989; Slutsker *et al.*, 1995; Paxton *et al.*, 1996). Much useful information is documented in the reports of relief agencies but these are not readily accessible. To remedy this shortcoming, a database of agency experiences has been produced for the Roll Back Malaria website (www.rbm.who.int). Several manuals also give guidance on malaria control in refugee situations (Thomson, 1995; Najera, 1996; Anon., 1997; Rozendaal, 1997).

STUDIES ON MALARIA IN AFGHAN AND KAREN REFUGEE CAMPS

The research series on Karen and Afghan refugees, while differing in objectives and emphasis, have produced considerable knowledge relevant not only to the study areas but also to complex emergencies in other countries. The research on Afghan refugees, led by Health-Net International, focuses on new approaches to personal protection and vector control and

on operational strategies for chronic emergencies. That on Karen refugees, led by the Shoklo Malaria Research Unit of the Wellcome–Mahidol University–Oxford Tropical Medicine Research Programme, focuses on multidrug-resistant malaria and on developing new therapies for managing resistant or severe malaria. Both research programmes take an epidemiological approach, and while the research on malaria in Afghans sometimes deals with drug resistance and clinical issues (Rowland *et al.*, 1997a; Shah *et al.*, 1997; Rowland and Durrani, 1999), that on the Karen refugees sometimes covers innovations in personal protection and disease control (Dolan *et al.*, 1993; Price *et al.*, 1996; Lindsay *et al.*, 1998). The strength of both programmes lies in their emphasis on operational research to produce the evidence to guide control. Their findings are taken up by NGO and UN agencies operating in the vicinity.

Afghan Refugees

EPIDEMIOLOGY AND TREATMENT

Afghan refugees have resided in Pakistan for over two decades. Over 3 million initially sought refuge after the Soviet invasion in 1979. Half were able to return home to safe areas in the early 1990s, after the fall of the Soviet-backed regime. But in the aftermath of the recent terrorist incidents in the United States, the number of Afghans trying to enter Pakistan may swell the refugee population to its former size. The refugees presently inhabit over 200 camps on the western border of Pakistan. The camps were sited on marginal land and many were waterlogged or adjoining rice cultivation, and hence prone to mosquito breeding. As the refugees were non-immune on arrival (Afghanistan had a successful malaria-control programme before the war; Suleman, 1988), malaria rapidly became a significant health problem. At the height of the epidemic among the refugees in 1990, over 150 000 cases were being diagnosed and treated each year by the combined healthcare services of the United Nations High Commission for Refugees (UNHCR), the government of Pakistan and NGO (Rowland, 1999).

About 30% of the cases were caused by *Plasmodium falciparum* and the rest by *P. vivax*.

Transmission of malaria in Pakistan is seasonal, and occurs mainly after the July–August monsoon (Rowland *et al.*, 2000). In subtropical climates there are usually two peaks of *P. vivax* malaria/year, with the first (spring) peak resulting from delayed attacks or relapses (Gill, 1938; Rowland *et al.*, 1997a). *Plasmodium falciparum* malaria shows a single peak, which comes after the summer peak of *P. vivax* because of the longer case-to-case incubation interval of *P. falciparum* (Macdonald, 1957; Bouma *et al.*, 1996a). Malaria in Pakistan shows long-term periodic cycles, the last significant epidemic having occurred in the mid-1970s (De Zulueta *et al.*, 1980). *Plasmodium falciparum* malaria is particularly unstable at the northern edge of its range, and can fluctuate markedly from year to year depending on climatic variation. High rainfall in autumn or above-average temperatures in November–December (a distinct trend in recent years) are key risk factors that enhance or prolong the transmission season in Pakistan (Bouma *et al.*, 1996a). Compounding the problem is the development of chloroquine resistance which, since the first reports in the mid-1980s (Fox *et al.*, 1985), has spread throughout the country (Shah *et al.*, 1997; Rowland *et al.*, 1997b). Chloroquine resistance is the main reason why *P. falciparum* malaria has become more prevalent during the last decade in Pakistan (Shah *et al.*, 1997), Afghanistan (Rab *et al.*, 2001), and neighbouring Tajikistan (Pitt *et al.*, 1998), whereas conflict and population upheaval are the factors responsible for the overall upsurge in malaria in the region (Kazmi and Pandit, 2001). Most (90%) of the cases of *P. falciparum* malaria among the Afghan refugees in western Pakistan are sensitive to sulfadoxine–pyrimethamine (Rowland *et al.*, 1997a) and the *P. vivax* malaria in this population is still sensitive to chloroquine (Rowland and Durrani, 1999).

Afghans are still sometimes accused of bringing malaria to Pakistan (Kazmi and Pandit, 2001). Refugees everywhere are frequently treated as scapegoats. The reality is that

Afghan arrivals in the early 1980s succumbed to malaria transmitted within Pakistan (Suleman, 1988). It was speculated at the time that poverty-stricken refugees were unable to benefit from zoophylaxis as they lacked the domestic animals necessary to divert mosquitoes away from humans (De Zulueta, 1989). It later transpired that the opposite was true: refugees who owned livestock, and camps with a high proportion of livestock-owning families, had a higher prevalence of malaria than people or camps with fewer domestic animals (Bouma and Rowland, 1995). The explanation seems to be that cattle provide mosquitoes with an easy source of blood, which leads to inflated vector populations (Nalin *et al.*, 1985), a significant proportion of which is attracted to feed on people sleeping outdoors close to their animals (Hewitt *et al.*, 1994). Nowadays most refugee families own livestock and malaria prevalence seems to differ little between Afghan and neighbouring Pakistani communities (Bouma, 1996).

Malaria Prevention and Control

INSECTICIDE-TREATED MATERIALS

TENT SPRAYING. A seemingly intractable problem—with important implications for malaria control in refugee camps elsewhere—was presented by nomadic refugees, living in tents, who migrated each spring from winter camps in the Punjab to high-altitude camps in the tribal areas of the North West Frontier province. Mobile populations pose a difficult problem because they transport malaria to unaffected areas, are hard to follow-up, and cannot be protected by that old mainstay of house spraying with residual insecticide. The advent of pyrethroid insecticides, highly toxic to mosquitoes in low concentrations, together with formulations that adhere to textiles, led to the prospect of vector control through treatment of tents. Spraying of inner surfaces with permethrin or deltamethrin produced a deposit that lasted for at least a year on double-sheeted tents (Hewitt *et al.*, 1995) whereas persistence on single-sheeted tents was limited to a few months, probably because of photo-decomposition (Bouma *et al.*, 1996b). A field trial of permethrin-treated tents pro-

vided 66% protective efficacy against *P. falciparum* malaria (Bouma *et al.*, 1996c). Treatment of tents is particularly effective against the endophilic (indoor-resting) species of mosquito found in South Asia and Africa. The technique may be less effective in regions where vectors are exophilic. Spraying or pre-treatment of tents should be standard practice whenever tents are distributed to refugees in malaria-endemic countries. All tents should be sprayed to give a mass protective effect (Hewitt *et al.*, 1995).

There is a trend towards issue of plastic tarpaulins rather than canvas tents, to reduce the cost of emergency aid. Whether plastic sheeting can be sprayed or impregnated to good effect is still being investigated.

INSECTICIDE-TREATED BEDNETS. When a government health structure is destroyed by war and people flee the country, those that remain behind have no option but to adopt personal protection. Insecticide-treated bednets (ITN) offer an attractive solution because users obtain some protection regardless of what other people are doing. However, transmission control and a mass effect on the local mosquito populations require a change of habits by the majority (Hewitt *et al.*, 1997). This cannot be guaranteed among peoples who have little or no tradition of using nets (e.g. those in South and Central Asia). Despite this reservation, the experiences in ITN deployment among Afghans give grounds for optimism. A household-randomized trial of ITN demonstrated 61% [95% confidence interval (CI) = 47%–71%] protective efficacy against *P. falciparum* malaria, 42% (CI = 32%–51%) efficacy against *P. vivax*, and high retention of nets after several years of use (Rowland *et al.*, 1996, 1997c). The results justified project expansion, and in recent years a significant proportion of the refugees has been inspired to purchase nets through social marketing schemes. As a public-health intervention, ITN sales through social marketing requires considerable investment or subsidy from donors. Per-capita costs decline with time because annual re-treatment (provided free by UNHCR) is only

10% of the initial outlay on nets (Rowland *et al.*, 1997c). This calculation assumes an emergency will persist for several years and that refugees and nets will be available for follow-up. When the camp breaks up, nets and owners are lost to re-treatment. It remains unclear whether the emigrants continue to make good use of the nets on returning home (Meek and Rowland, 1998).

Nets are more likely to be appreciated and used if recipients bear some of the costs. This also reduces the level of investment needed from donors. Cost recovery, however, may not be feasible or ethical in acute-phase emergencies when refugees lack possessions or means. Free distribution of nets in acute emergencies or epidemics, though practised increasingly by aid agencies, remains controversial because families and communities are usually unwilling to start paying for nets after the acute emergency, with dire consequences for coverage, cost recovery and sustainability (WHO, 1999). Chronic conflict or post-conflict conditions, during which livelihoods improve, offer better prospects for social marketing. Social marketing of ITN by a consortium of healthcare NGO has been operating in eastern and southern Afghanistan since 1993, and over a million inhabitants, about 20% of the population, are now protected (Rowland, 1999).

PERMETHRIN-TREATED CLOTHING OR BEDDING.

Treatment of blankets or top-sheets with permethrin is a promising option for refugees sheltering under plastic sheeting or other makeshift materials. A household-randomized trial of treated top-sheets, blankets and Islamic head-and-body veils (*chaddars*) gave 64% (CI = 35%–80%) protective efficacy against *P. falciparum* attack and 38% (CI = 0%–64%) efficacy against *P. vivax* attack among children and teenagers (*chaddars* are used by women and men as blankets at night) (Rowland *et al.*, 1999). A single treatment was protective for 4 months. This new approach to self-protection has great potential during epidemics and the acute phase of emergencies because blankets and sheets are always needed in such situations and treatment would give protection in

all types of shelter. The outlay is only 15% of that needed for an ITN. Permethrin is favoured because it is repellent, safe and has no side-effects.

The encouraging results with malaria led to a comparison of the impact of treated blankets and bednets against *Leishmania tropica*, the insect-borne cause of cutaneous leishmaniasis, during a city-wide epidemic in war-torn Kabul, capital of Afghanistan. Although treated blankets were equivalent to the treated nets in preventing disease, the treated nets were the more popular intervention (Reyburn *et al.*, 2000). Hence treated blankets are favoured for short-term epidemic control and ITN as a long-term solution.

OTHER PERSONAL-PROTECTION METHODS

Other personal-protection methods tested in refugee camps (Hewitt *et al.*, 1996) include electric fans (27% reduction in mosquito biting), pyrethrum coils (36% reduction), pyrethroid-vaporizing mats (56% reduction) and permethrin-treated curtains (65% reduction). Treated curtains are especially promising because they are cheap, require no electricity and are the most effective of these other methods. As Afghans tend to stop using their ITN when they move indoors in the autumn, despite the continuing risk of *P. falciparum* infection, they are then encouraged to use the nets as curtains. Techniques that require recurrent household expenditure, such as the use of mosquito coils, seem less promising.

INDOOR SPRAYING OF RESIDUAL INSECTICIDE

Emergencies require vertical provision of aid, and under such circumstances malaria control is best served by methods that would be unsustainable under peacetime conditions. Indoor residual spraying (IRS) is the method most often used by the UNHCR when displaced populations inhabit mud huts or houses and when anopheline vectors are known to rest indoors (Najera, 1996; Meek and Rowland, 1998). IRS is primarily a community-protection measure and a mass effect on the density of the local populations of vectors requires the majority of dwellings to be

sprayed. Many species of vector are resistant to DDT and organophosphate insecticides, so the choice of insecticide must be carefully considered. When campaigns are well run, IRS is no less effective than ITN, as was demonstrated in comparative trials in refugee camps in Pakistan and Tanzania (Curtis *et al.*, 1999; Rowland, 1999). When using malathion and lambda-cyhalothrin in Afghan camps, the protective efficacy offered by IRS was 50%–60% against *P. falciparum* malaria and 40%–50% against *P. vivax* (Rowland *et al.*, 1994, 1997b). As a result of recurrent, annual, IRS campaigns by the UNHCR, targeted against the more malarious camps, the overall malaria burden in the refugee population of the North West Frontier province of Pakistan was reduced by an estimated 87 000 cases between 1991 and 1995 (Rowland, 1999). IRS campaigns require good organization to be effective: timely delivery of insecticide and pumps (usually shipped or airfreighted from abroad); training of sprayers in the safe handling of the insecticides and in thorough spraying; and proper supervision. In chaotic acute-phase emergencies, the organization of IRS campaigns rarely runs smoothly, and it is very easy to miss the window of opportunity at the beginning of the transmission season when spraying exerts maximum effect (Rowland *et al.*, 1997). When applied as a reactive measure against a rising epidemic, IRS campaigns have less impact (Rowland, 1999). Over the long-term, recurrent IRS campaigns are an expensive preventive strategy because costs do not decrease with time. If the emergency seems destined to continue for many years ITN are a more cost-effective and sustainable solution because annual re-treatment of nets uses less insecticide than IRS (although start-up costs are higher).

LIVESTOCK SPONGING

International aid always declines when acute emergencies become chronic refugee situations, prompting the need for more cost-effective solutions. In South Asia most species of anopheline are zoophilic, tending to feed on cattle rather than humans most of the time. This led to the notion of applying insecticide

to the surfaces of domestic livestock (cattle and goats) in the expectation they would act as toxic bait. In entomological trials, deltamethrin proved effective in killing mosquitoes for up to 4 weeks after treating cattle (Hewitt and Rowland, 1999). A community-randomized trial in which refugee communities sponged their domestic animals with deltamethrin four times a year reduced the incidence of *P. falciparum* malaria by 56% (CI = 14%–78%; Rowland *et al.*, 2001). Indoor spraying of houses in the same group of camps in previous years used five times as much insecticide for about the same impact (Rowland *et al.*, 1997b).

Livestock sponging is now standard practice in many Afghan camps, and has the potential to control epidemic malaria in any region of the world where vectors are zoophilic.

Karen Refugees

Malaria on the Thai–Burmese border differs in several important respects from that in Pakistan–Afghanistan. *Plasmodium falciparum* predominates and is highly drug resistant, and the vectors bite early and rest outdoors. Although *P. vivax* remains sensitive to chloroquine (Luxemburger *et al.*, 1999), malaria control among the Karen refugees requires a different approach to the vector-control approach applied in Pakistan–Afghanistan.

EPIDEMIOLOGY AND DIAGNOSIS

At the start of the malaria-research programme in 1986, 70% of the malarial infections in the Karen camps were of *P. falciparum*. The children each experienced one or two malarial infections annually, of which 68% were symptomatic. *Plasmodium vivax* malaria was most common in young children whereas *P. falciparum* peaked in adults aged 20–29 years. As in the Afghan camps, the malaria tended to be clustered in households (Luxemburger *et al.*, 1996). The risks of developing severe malaria and of malaria-attributable death decreased with age. Curiously, severe malaria was less common among those with mixed infections of *P. vivax* and *P. falciparum* than among those only infected with *P. falciparum*; *P. vivax* may attenuate the

severity of *P. falciparum* malaria (Luxemburger *et al.*, 1997). In the late 1980s, malaria represented the first cause of morbidity (45% of consultations) and mortality (15% of deaths) in the camps. The burden was especially heavy in pregnancy and it was estimated that each year 1% of all pregnant women in the camps died of cerebral malaria. This cause of mortality was only prevented by systematic weekly screening of all pregnant women. The data collected provided the first detailed description of the impact of *P. falciparum* malaria in pregnancy in an area of low and unstable malaria transmission (Nosten *et al.*, 1991b). Several years later, the database allowed the first description of the adverse effects of *P. vivax* in pregnancy (Nosten *et al.*, 1999a).

A study on the predictive value of clinical symptoms (or their combinations) in the diagnosis of malaria indicated that the best algorithm would fail in 51% of cases while 30% of non-malaria cases would be mistaken for malaria and wrongly treated (Luxemburger *et al.*, 1998). The results of this study demonstrated the importance of confirming the diagnosis of malaria by microscopy (or rapid test).

TREATMENT OF MALARIA

The *P. falciparum* in South-east Asia is fully resistant to chloroquine and sulfadoxine-pyrimethamine (SP) and these antimalarials cannot be used for treatment. Despite this, the combination of SP and mefloquine (30/1.5/15 mg/kg; Fansimef[®]) was deployed in 1984 in Thailand and introduced one year later in the Karen refugee camps. Initially the efficacy was satisfactory (Nosten *et al.*, 1987) but, despite strict observance of the recommendations (the drug was prescribed only in confirmed cases and use was strictly controlled), resistance developed rapidly (Nosten *et al.*, 1991a). The fixed combination was abandoned in the Karen camps and soon after in Thailand and replaced with high dose (25 mg/kg) mefloquine (Ter Kuile *et al.*, 1992; Smithuis *et al.*, 1993). However, because of a continued decline in the efficacy of mefloquine (Luxemburger *et al.*, 1996), alternative treatments were sought.

A paired, randomized trial of halofantrine (24 mg/kg) and mefloquine (25 mg/kg) gave failure rates of 35% and 10%, respectively (Ter Kuile *et al.*, 1993). Unfortunately, not only was cross resistance between the two compounds a problem but the halofantrine also produced a previously unknown but potentially lethal cardiotoxicity (Nosten *et al.*, 1993) and its use is no longer recommended (Nosten and Price, 1995).

Against the backdrop of increasing resistance of *P. falciparum* to mefloquine, clinical trials started in 1991 on the use of the artemisinin derivatives, a novel class of antimalarial emanating from China. These compounds are the most potent antimalarials known. To date, over 10 000 patients have been enrolled in prospective studies (the largest drug trials on antimalarials ever) involving these drugs in Karen camps. The artemisinin derivatives are very effective and safe (Nosten *et al.*, 1994a; Price *et al.*, 1995, 1996, 1997, 1999), and their speed of action is particularly useful in the treatment of patients with high parasitaemias (Luxemburger *et al.*, 1995). Most importantly, these antimalarials were shown to have an impact on the transmission of malaria through their action on gametocytes (Price *et al.*, 1996). In combination with high-dose mefloquine, the artemisinin derivatives have reduced malaria incidence in the Karen camps by 90% and halted the progression of mefloquine resistance (Brockman *et al.*, 2000; Nosten *et al.*, 2000). Nevertheless, mefloquine continues to be used 'unprotected' by artesunate outside the camps, and selection of resistance is bound to accelerate, making the search for other treatments a priority.

A new combination of luméfantrine and artemether (Riamet[®]) has shown excellent efficacy and the same effect on gametocyte carriage as (and a better tolerability than) that of mefloquine-artesunate (Van Vugt *et al.*, 1998, 1999).

Finally, the results of studies in this setting have shown that artemether, one of the artemisinin derivatives, could be administered intra-rectally as an effective treatment of malaria (Teja-Isavadharm *et al.*, 1996; Nosten

et al., 1998). This opens important possibilities for therapy in the peripheral areas where parenteral treatment is not available. Although the treatment of *P. falciparum* malaria with artemisinin-based combinations has allowed some respite, difficulties remain for the treatment of pregnant women. Although mefloquine and artesunate were both effective among such women (McGready *et al.*, 1998a, b), mefloquine was associated with an increased risk of stillbirth and abandoned for treatment during pregnancy (Nosten *et al.*, 1999b).

CHEMOPROPHYLAXIS AND OTHER PERSONAL PROTECTION

Despite the existence of low-level resistance, use of mefloquine as a prophylaxis during the second half of pregnancy gave 86% protection, reduced anaemia, and improved birth-weight in gravidae I, II and III (Nosten *et al.*, 1994b). However, the emergence of strains of *P. falciparum* that were highly resistant to mefloquine and the discovery of the increased risk of stillbirth in mefloquine-treated women meant that mefloquine prophylaxis was never deployed in the refugee camps. Because of the multiple drug resistance, there is presently no suitable drug for prophylaxis during pregnancy in this area.

Although bednets impregnated with permethrin proved effective in the protection of schoolchildren living in the camps, at least in a strictly supervised, controlled trial (Luxemburger *et al.*, 1994), they were less effective in protecting the pregnant women (Dolan *et al.*, 1993) and have not been widely deployed until recently. Skin repellent (DEET) mixed with a local cosmetic (*Tanakha*) proved effective against mosquito bites in a pilot study (Lindsay *et al.*, 1998). That a large randomized trial failed to demonstrate this mixture's effectiveness in protecting pregnant women (McGready *et al.*, 2001) was probably largely the result of a dramatic drop in the overall incidence of malaria, following the widespread use of the artemisinin-based drug combinations. The much-publicised SPf66 malaria vaccine was also studied in Karen children living in the camps but proved ineffective (Nosten *et*

al., 1996) and further development was abandoned.

CONCLUSIONS

Complex emergencies are dynamic, evolving through acute to chronic and then post-conflict phases. The dynamics of malaria also change, in parallel with socio-political developments, and different approaches to treatment and prevention are needed at each stage of the crisis. The series of studies on Karen and Afghan refugees show that operational research, integrated into a regular malaria-control programme, can provide the evidence base that leads to sustainable reductions in malaria. The information generated by the two research programmes has value beyond refugee situations. For example, the efficacy of treatment with artemisinin-based combinations, which was pioneered in the Karen camps, is now being investigated elsewhere in Asia and in Africa and South America, following endorsement by the World Health Organization.

Although operational research (OR) is given low priority in emergencies, it can help to inform and improve approaches to malaria control. It can answer questions specific to the emergency, identify locally effective treatments and culturally appropriate methods of malaria prevention, and highlight the social and behavioural factors that contribute to the problem or limit the effectiveness of control. It is hoped that the relevant agencies will recognize the potential of OR and try to include simple, related study designs into their control projects rather than see OR as the domain of outside specialists. Agencies are well placed to contribute to the solving of outstanding operational issues in malaria control. The hardest challenge is the control of malaria in the acute phase of an emergency, when mortality rates are high and health services rudimentary. Agencies' priorities are rightly focused then on saving lives but it is also recognized that the acute phase is the one that needs more answers, new solutions, and hence more research.

Ethical issues must also be addressed when working with refugee populations that are rightly considered fragile. This applies to all organizations working in these situations—UN agencies, NGO and others. In the experiences presented here, all necessary steps were taken to ensure that the rights of individuals to participate in surveys, trials and other studies were protected. In practice, all the research programmes had to be approved by the ethical committees of all the institutions involved: Refugee Committees, University Committees, UNHCR, WHO, the Walter Reed Army Institute of Research, the U.S. National Institutes of Health, and any other supporting bodies. Importantly, most of the work generated by these programmes was carried out by workers from the communities where the studies were conducted, thus directly involving the people affected by malaria in the effort to control it.

The lack of published documentation from international agencies—about what has been

tried, what has worked and what has failed—leaves a significant gap in our knowledge of malaria control in complex emergencies. To improve future responses, a critical review of past practices would provide important lessons.

ACKNOWLEDGEMENTS. HealthNet International's Malaria Programme is supported by the European Commission (DG1), the United Nations High Commissioner for Refugees, and WHO/UNDP/World Bank Special Programme for Research and Training in Tropical Diseases (project no. 960662). M.R. is supported by the U.K.'s Department for International Development and the Gates Foundation. F.N. and the Shoklo Malaria Research Unit of the Wellcome–Mahidol University–Oxford Tropical Medicine Research Programme are supported by the Wellcome Trust. However, none of these donors can accept responsibility for any information provided or views expressed.

REFERENCES

- ANON. (1995). *The State of the World's Refugees—in Search of Solutions*. Oxford: Oxford University Press.
- ANON. (1997). *Refugee Health Care: an Approach to Emergency Situations*. London: Macmillan Education.
- BOUMA, M. J. (1996). *Epidemiology and control of malaria in northern Pakistan with special reference to Afghan refugees and the El-Niño southern oscillation*. Ph.D. thesis, University of London, U.K.
- BOUMA, M. & ROWLAND, M. (1995). Failure of passive zoophylaxis: malaria is associated with cattle ownership in Pakistan. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **89**, 351–353.
- BOUMA, M. J., DYE, C. & VAN DER KAAJ, H. J. (1996a). Falciparum malaria and climate change in the North West Frontier province of Pakistan. *American Journal of Tropical Medicine and Hygiene*, **55**, 131–137.
- BOUMA, M. J., PARVEZ, S. D., NESBIT, R. & SONDRUP, H. E. (1996b). Rapid decomposition of permethrin in the outer fly of an experimental tent in Pakistan. *Journal of the American Mosquito Control Association*, **12**, 125–129.
- BOUMA, M. J., PARVEZ, S. D., NESBIT, R., WINKLER, A. M. (1996c). Malaria control using permethrin applied to tents of nomadic Afghan refugees in northern Pakistan. *Bulletin of the World Health Organization*, **74**, 413–421.
- BROCKMAN, A., PRICE, R., VAN VUGT, M., HEPPNER, D. G., WALSH, D., SOOKTO, P., WIMONWATTRAWATEE, T., LOOAREESUWAN, S., WHITE, N. J. & NOSTEN, F. (2000). *Plasmodium falciparum* antimalarial drug susceptibility on the northwestern border of Thailand during five years of extensive artesunate–mefloquine use. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **94**, 537–544.
- CURTIS, C. F., MNZAVA, A. E. P., MISRA, S. & ROWLAND, M. (1999). Malaria control: bednets or spraying? Summary of the presentations and the discussion. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **93**, 460.
- DE ZULUETA, J. (1989). *Malaria in Afghan Refugees*. Geneva: United Nations High Commissioner for Refugees.
- DE ZULUETA, J., MUJTABA, S. M. & SHAH, I. H. (1980). Malaria control and long-term periodicity of the disease in Pakistan. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **74**, 624–632.

- DOLAN, G., TER KUILE, F. O., JACOUTOT, V., WHITE, N. J., LUXEMBURGER, C., MALANKIRII, L., CHONGSUPHAJASIDDHI, T. & NOSTEN, F. (1993). Bed nets for the prevention of malaria and anaemia in pregnancy. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **87**, 620–626.
- FOX, E., KHALIQ, A. A., SARWAR, M. & STRICKLAND, G. T. (1985). Chloroquine-resistant *Plasmodium falciparum*: now in Pakistani Punjab. *Lancet*, **i**, 1432–1434.
- GILL, C. A. (1938). *The Seasonal Periodicity of Malaria and the Mechanism of the Epidemic Wave*. London: Churchill.
- GLASS, R. I., CATES, W., NIEBURG, P., DAVIS, C., RUSSBACH, R., NOTHDURFT, H., PEEL, S. & TURNBULL, R. (1980). Rapid assessment of health status and preventive-medicine needs of newly arrived Kampuchean refugees, Sa Kao, Thailand. *Lancet*, **i**, 868–872.
- GUERRERO, I. C., CHIN, W. & COLLINS, W. E. (1982). A survey of malaria in Indochinese refugees arriving in the United States, 1980. *American Journal of Tropical Medicine and Hygiene*, **31**, 897–901.
- GUTHMANN, J. P., CETRE, C., SUZAN, F., DAROVARE, S. & MORIN, F. (1996). Field research, relief work and war: does chloroquine-resistance occur in displaced populations of southern Sudan? *Tropical Doctor*, **26**, 89–90.
- HEWITT, S. & ROWLAND, M. (1999). Control of zoophilic malaria vectors by applying pyrethroid insecticides to cattle. *Tropical Medicine and International Health*, **4**, 481–486.
- HEWITT, S., KAMAL, M., NASIR, M. & ROWLAND, M. (1994). An entomological investigation of the likely impact of cattle ownership on malaria in an Afghan refugee camp in the North West Frontier province of Pakistan. *Medical and Veterinary Entomology*, **8**, 160–164.
- HEWITT, S., ROWLAND, M., NASIR, M., KAMAL, M. & KEMP, E. (1995). Pyrethroid sprayed tents for malaria control: an entomological evaluation in Pakistan's North West Frontier province. *Medical and Veterinary Entomology*, **9**, 344–352.
- HEWITT, S. E., FARHAN, M., URHAMAN, H., MUHAMMAD, N., KAMAL, M. & ROWLAND, M. W. (1996). Self-protection from malaria vectors in Pakistan: an evaluation of popular existing methods and appropriate new techniques in Afghan refugee communities. *Annals of Tropical Medicine and Parasitology*, **90**, 337–344.
- HEWITT, S., FORD, E., URHAMAN, H., MOHAMMAD, N. & ROWLAND, M. (1997). The effect of bed nets on unprotected people: open-air studies in an Afghan refugee village. *Bulletin of Entomological Research*, **87**, 455–459.
- HURWITZ, E. S., JOHNSON, D. & CAMPBELL, C. C. (1981). Resistance of *Plasmodium falciparum* malaria to sulfadoxine-pyrimethamine ('Fansidar') in a refugee camp in Thailand. *Lancet*, **229**, 1068–1070.
- KAZMI, J. H. & PANDIT, K. (2001). Disease and displacement: the impact of refugee movements on the geography of malaria in NWFP, Pakistan. *Social Science and Medicine*, **52**, 1043–1055.
- LIENHARDT, C., GHEBRAY, R., CANDOLFI, E., KIEN, T. & HEDLIN, G. (1990). Malaria in refugee camps in eastern Sudan: a sero-epidemiological approach. *Annals of Tropical Medicine and Parasitology*, **84**, 215–222.
- LINDSAY, S. W., EWALD, J. A., SAMUNG, Y., APIWATHNASORN, C. & NOSTEN, F. (1998). Thanaka and deet mixture as a mosquito repellent for use by Karen women. *Medical and Veterinary Entomology*, **12**, 295–301.
- LUXEMBURGER, C., PEREA, W. A., DELMAS, G., PRUJA, C. & MOREN, A. (1994). Permethrin impregnated bed nets for the prevention of malaria in schoolchildren on the Thai–Burmese border. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **88**, 155–159.
- LUXEMBURGER, C., THWAL, K. L., WHITE, N. J., WEBSTER, H. K., KYLE, D. E., MAELANKIRRI, L., CHONGSUPHAJASIDDHI, T. & NOSTEN, F. (1996). The epidemiology of malaria in a Karen population on the western border of Thailand. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **90**, 105–111.
- LUXEMBURGER, C., RICCI, F., NOSTEN, F., RAIMOND, D., BATHET, S. & WHITE, N. J. (1997). The epidemiology of severe malaria in an area of low transmission in Thailand. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **91**, 256–262.
- LUXEMBURGER, C., NOSTEN, F., KYLE, D., HKIRIJAROEN, L., CHONGSUPHAJASIDDHI, T. & WHITE, N. J. (1998). Clinical features cannot predict a diagnosis of malaria or differentiate the infecting species in children living in an area of low transmission. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **92**, 45–49.
- LUXEMBURGER, C., VAN VUGT, M., JONATHAN, S., MCGREADY, R., LOOAREESUWAN, S., WHITE, N. J. &

- NOSTEN, F. (1999). Treatment of vivax malaria on the western border of Thailand. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **93**, 433–438.
- MACDONALD, G. (1957). *The Epidemiology and Control of Malaria*. London: Oxford University Press.
- MCGREADY, R., CHO, T., CHO, J. J., SIMPSON, J., LUXEMBURGER, C., DUBOWITZ, L., LOOAREESUWAN, S., WHITE, N. J. & NOSTEN, F. (1998a). Artemisinin derivatives in the treatment of *P. falciparum* malaria in pregnancy. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **92**, 433.
- MCGREADY, R., CHO, T., HKIRIJAROEN, L., SIMPSON, J., CHONGSUPHAJASIDDHI, T., WHITE, N. J. & NOSTEN, F. (1998b). Quinine and mefloquine in the treatment of multidrug-resistant *Plasmodium falciparum* malaria in pregnancy. *Annals of Tropical Medicine and Parasitology*, **92**, 643–653.
- MCGREADY, R., SIMPSON, J. A., HTWAY, M., WHITE, N. J., NOSTEN, F. & LINDSAY, S. W. (2001). A double-blind randomized therapeutic trial of insect repellents for the prevention of malaria in pregnancy. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **95**, 137–138.
- MEEK, S. R. (1988). Epidemiology of malaria in displaced Khmers on the Thai–Kampuchean border. *Southeast Asian Journal of Tropical Medicine and Public Health*, **19**, 243–252.
- MEEK, S. & ROWLAND, M. (1998). Malaria in emergency situations. *World Health*, **3**, 22–23.
- NAJERA, J. A. (1996). *Malaria Control among Refugees and Displaced Populations*. Document CTD/MAL/96.6. Geneva: World Health Organization.
- NAJERA, J. A., KOUZNETZOV, R. L. & DELACOLLETTE, C. (1998). *Malaria Epidemics: Detection and Control, Forecasting and Prevention*. Document WHO/MAL/98.1084. Geneva: World Health Organization.
- NALIN, D. R., MAHOOD, F., RATHOR, H., MUTTALIB, A., SAKAI, R., CHOWDHRY, M. A., SAFDAR, G., UL HAQ, I., MUNIR, M. & SULEIMAN, M. (1985). A point survey of periurban and urban malaria in Karachi. *Journal of Tropical Medicine and Hygiene*, **88**, 7–15.
- NOSTEN, F. (1998). Artemisinin: large community studies. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **88** (Suppl. 1), S45–S46.
- NOSTEN, F. & PRICE, R. N. (1995). New antimalarials. A risk–benefit analysis. *Drug Safety*, **12**, 264–273.
- NOSTEN, F., IMVITHAYA, S., VINCENTI, M., DELMAS, G., LEBIHAN, G., HAUSLER, B. & WHITE, N. J. (1987). Malaria on the Thai–Burmese border: treatment of 5192 patients with mefloquine–sulfadoxine–pyrimethamine. *Bulletin of the World Health Organization*, **65**, 891–896.
- NOSTEN, F., TER KUILE, F., CHONGSUPHAJASIDDHI, T., LUXEMBURGER, C., WEBSTER, H. K., EDSTEIN, M., PHAIPUN, L., THWAI, K. L. & WHITE, N. J. (1991a). Mefloquine-resistant falciparum malaria on the Thai–Burmese border. *Lancet*, **337**, 1140–1143.
- NOSTEN, F., TER KUILE, F., MAELANKIRRI, L., DECLUDT, B. & WHITE, N. J. (1991b). Malaria during pregnancy in an area of unstable endemicity. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **85**, 424–429.
- NOSTEN, F., TER KUILE, F., LUXEMBURGER, C., WOODROW, C., KYLE, D. E., CHONGSUPHAJASIDDHI, T. & WHITE, N. J. (1993). Cardiac effects of antimalarial treatment with halofantrine. *Lancet*, **341**, 1054–1056.
- NOSTEN, F., LUXEMBURGER, C., TER KUILE, F., WOODROW, C., EH, J. P., CHONGSUPHAJASIDDHI, T. & WHITE, N. J. (1994a). Treatment of multidrug-resistant *Plasmodium falciparum* malaria with 3-day artesunate–mefloquine combination. *Journal of Infectious Diseases*, **170**, 971–977.
- NOSTEN, F., TER KUILE, F., MAELANKIRI, L., CHONGSUPHAJASIDDHI, T., NOPDONRATTAKOON, L., TANGKITCHOT, S., BOUDREAU, E., BUNNAG, D. & WHITE, N. J. (1994b). Mefloquine prophylaxis prevents malaria during pregnancy: a double-blind, placebo-controlled study. *Journal of Infectious Diseases*, **169**, 595–603.
- NOSTEN, F., LUXEMBURGER, C., KYLE, D. E., BALLOU, W. R., WITTES, J., WAH, E., CHONGSUPHAJASIDDHI, T., GORDON, D. M., WHITE, N. J., SADOFF, J. C. & HEPPNER, D. G. (1996). Randomised double-blind placebo-controlled trial of SPf66 malaria vaccine in children in northwestern Thailand. Shoklo SPf66 Malaria Vaccine Trial Group. *Lancet*, **348**, 701–707.
- NOSTEN, F., VAN VUGT, M. & WHITE, N. J. (1998). Intrarectal artemisinin derivatives. *Médecine Tropicale*, **58**, 63–64.
- NOSTEN, F., MCGREADY, R., SIMPSON, J., THWAI, K. L., BALKAN, S., CHO, T., HKIRIJAROEN, L., LOOAREESUWAN, S. & WHITE, N. J. (1999a). Effects of *Plasmodium vivax* malaria in pregnancy. *Lancet*, **354**, 346–349.

- NOSTEN, F., VINCENTI, M., SIMPSON, J., YEI, P., THWAI, K. L., DE VRIES, A., CHONGSUPHAJASIDDHI, T. & WHITE, N. J. (1999b). The effects of mefloquine treatment in pregnancy. *Clinical and Infectious Diseases*, **28**, 808–815.
- NOSTEN, F., VAN VUGT, M., PRICE, R., LUXEMBURGER, C., THWAI, K. L., BROCKMAN, A., MCGREADY, R., TER KUILE, F., LOOAREESUWAN, S. & WHITE, N. J. (2000). Effects of artesunate–mefloquine combination on incidence of *Plasmodium falciparum* malaria and mefloquine resistance in western Thailand: a prospective study. *Lancet*, **356**, 297–302.
- PAXTON, L. A., SLUTSKER, L., SCHULTZ, L. J., LUBY, S. P., MERIWETHER, R., MATSON, P. & SULZER, A. J. (1996). Imported malaria in Montagnard refugees settling in North Carolina: implications for prevention and control. *American Journal of Tropical Medicine and Hygiene*, **54**, 54–57.
- PITT, S., PEARCY, B. E., STEVENS, R. H., SHARIPOV, A., SATAROV, K. & BANATVALA, N. (1998). War in Tajikistan and re-emergence of *Plasmodium falciparum*. *Lancet*, **352**, 1279.
- PRICE, R. N., NOSTEN, F., LUXEMBURGER, C., KHAM, A., BROCKMAN, A., CHONGSUPHAJASIDDHI, T. & WHITE, N. J. (1995). Artesunate versus artemether in combination with mefloquine for the treatment of multidrug-resistant falciparum malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **89**, 523–527.
- PRICE, R. N., NOSTEN, F., LUXEMBURGER, C., TER KUILE, F., PHAIPUN, L., CHONGSUPHAJASIDDHI, T. & WHITE, N. J. (1996). Effects of artemisinin derivatives on malaria transmissibility. *Lancet*, **347**, 1654–1658.
- PRICE, R. N., NOSTEN, F., LUXEMBURGER, C., VAN VUGT, M., PHAIPUN, L., CHONGSUPHAJASIDDHI, T. & WHITE, N. J. (1997). Artesunate/mefloquine treatment of multi-drug resistant falciparum malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **91**, 574–577.
- PRICE, R. N., VAN VUGT, M., NOSTEN, F., LUXEMBURGER, C., SIMPSON, J., PHAIPUN, L., CHONGSUPHAJASIDDHI, T. & WHITE, N. J. (1999). Adverse effects in patients with acute falciparum malaria treated with artemisinin derivative. *American Journal of Tropical Medicine and Hygiene*, **60**, 547–555.
- RAB, M. A., FREEMAN, T. W., DURRANI, N., DE POERCK, D. & ROWLAND, M. W. (2001). Resistance of *Plasmodium falciparum* malaria to chloroquine is widespread in eastern Afghanistan. *Annals of Tropical Medicine and Parasitology*, **95**, 41–46.
- REY, J. L., CAVALLO, J. D., MILLELIRI, J. M., L'HOEST, S., SOARES, J. L., PINY, N., COUE, J. C. & JOUAN, A. (1996). Fever of unknown origin (FUO) in the camps of Rwandan refugees in the Goma region of in Zaire (September 1994). *Bulletin de la Société de Pathologie Exotique*, **89**, 204–208.
- REYBURN, H., ASHFORD, R., MOHSEN, M., HEWITT, S. & ROWLAND, M. (2000). A randomised controlled trial of insecticide treated bed nets and top-sheets, and residual spraying of interior rooms for the prevention of anthroponotic cutaneous leishmaniasis in Kabul, Afghanistan. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **94**, 361–366.
- ROWLAND, M. (1999). Malaria control: bednets or spraying? Malaria control in the Afghan refugee camps of western Pakistan. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **93**, 458–459.
- ROWLAND, M. & DURRANI, N. (1999). Randomized controlled trials of 5- and 14-days primaquine therapy against relapses of vivax malaria in an Afghan refugee settlement in Pakistan. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **93**, 641–643.
- ROWLAND, M., HEWITT, S. & DURRANI, N. (1994). Malaria prevalence surveys in refugee camps sprayed with malathion and lambda-cyhalothrin. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **88**, 378–379.
- ROWLAND, M., BOUMA, M., DUCORNEZ, D., DURRANI, N., ROZENDAAL, J., SCHAPIRA, A. & SONDRP, E. (1996). Pyrethroid impregnated bed nets for self protection from malaria for Afghan refugees. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **90**, 357–361.
- ROWLAND, M., DURRANI, N., HEWITT, S. & SONDRP, E. (1997a). Resistance of falciparum malaria to chloroquine and sulfadoxine–pyrimethamine in Afghan refugee settlements in western Pakistan: surveys by the general health services using a simplified *in vivo* test. *Tropical Medicine and International Health*, **2**, 1049–1056.
- ROWLAND, M., HEWITT, S. & DURRANI, N. (1997b). Transmission and control of vivax malaria in Afghan refugee villages in Pakistan. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **91**, 252–255.

- ROWLAND, M., HEWITT, S., DURRANI, N., SALEH, P., BOUMA, M. & SONDRP, E. (1997c). Sustainability of pyrethroid impregnated bed nets for malaria control in Afghan communities. *Bulletin of the World Health Organization*, **75**, 23–29.
- ROWLAND, M., DURRANI, N., HEWITT, S., MOHAMMED, N., BOUMA, M., CARNEIRO, I., ROZENDAAL, J. & SCHAPIRA, A. (1999). Permethrin treated chaddars and top-sheets: appropriate technology for protection against malaria in Afghanistan and other complex emergencies. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **93**, 465–472.
- ROWLAND, M., CARNEIRO, I., IQBAL, J. & CHEVASSE, D. (2000). Indoor residual spraying with alphacypermethrin controls malaria in Pakistan: a community-randomised trial. *Tropical Medicine and International Health*, **5**, 472–481.
- ROWLAND, M., DURRANI, N., KENWARD, M., NASIR, M., URAHMAN, H. & HEWITT, S. (2001). Control of malaria by applying deltamethrin insecticide to cattle: a community-randomised trial in Pakistan. *Lancet*, **357**, 1837–1841.
- ROZENDAAL, J. A. (1997). *Vector Control: Methods for Use by Individuals and Communities*. Geneva: World Health Organization.
- SCHULTZ, M. G. (1989). Malaria in migrants and travellers. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **83** (Suppl.), 31–34.
- SHAH, I., ROWLAND, M., MEHMOOD, P., MUJAHID, C., RAZIQ, F., HEWITT, S. & DURRANI, N. (1997). Chloroquine resistance in Pakistan and the upsurge of falciparum malaria in Pakistani and Afghan refugee populations. *Annals of Tropical Medicine and Parasitology*, **91**, 591–602.
- SHEARS, P., BERRY, A. M., MURPHY, R. & NABIL, M. A. (1987). Epidemiological assessment of the health and nutrition of Ethiopian refugees in emergency camps in Sudan, 1985. *British Medical Journal (Clinical Research and Education)*, **295**, 314–318.
- SIMMONDS, S., VAUGHN, P. & GUNN, S. W. (1983). *Refugee Community Health Care*. Oxford: Oxford University Press.
- SLUTSKER, L., TIPPLE, M., KEANE, V., MCCANCE, C. & CAMPBELL, C. C. (1995). Malaria in east African refugees resettling to the United States: development of strategies to reduce the risk of imported malaria. *Journal of Infectious Diseases*, **171**, 489–493.
- SMITHUIS, F. M., VAN WOENSEL, J. B., NORDLANDER, E., VANTHA, W. S. & TER KUILE, F. O. (1993). Comparison of two mefloquine regimens for treatment of *Plasmodium falciparum* malaria on the northeastern Thai–Cambodian border. *Antimicrobial Agents and Chemotherapy*, **37**, 1977–1981.
- SULEMAN, M. (1988). Malaria in Afghan refugees in Pakistan. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **82**, 44–47.
- TEJA-ISAVADHARM, P., NOSTEN, F., KYLE, D. E., LUXEMBURGER, C., TER KUILE, F., PEGGINS, J. O., BREWER, T. G. & WHITE, N. J. (1996). Comparative bioavailability of oral, rectal, and intramuscular artemether in healthy subjects: use of simultaneous measurement by high performance liquid chromatography and bioassay. *British Journal of Clinical Pharmacology*, **42**, 599–604.
- TER KUILE, F., NOSTEN, F., THEREN, M., LUXEMBURGER, C., EDSTEIN, M. D., CHONGSUPHAJASIDDHI, T., PHAIPUN, L., WEBSTER, H. K. & WHITE, N. J. (1992). High-dose mefloquine in the treatment of multidrug-resistant falciparum malaria. *Journal of Infectious Diseases*, **166**, 1393–1400.
- TER KUILE, F., DOLAN, G., NOSTEN, F., EDSTEIN, M. D., LUXEMBURGER, C., PHAIPUN, L., CHONGSUPHAJASIDDHI, T., WEBSTER, H. K. & WHITE, N. J. (1993). Halofantrine versus mefloquine in treatment of multidrug-resistant falciparum malaria. *Lancet*, **341**, 1044–1049.
- THOMSON, M. C. (1995). *Disease Prevention Through Vector Control: Guidelines for Relief Organisations*. Oxford, U.K.: Oxfam.
- TOOLE, M. J. & WALDMAN, R. J. (1990). Prevention of excess mortality in refugee and displaced populations in developing countries. *Journal of the American Medical Association*, **263**, 3296–3302.
- TOOLE, M. J. & WALDMAN, R. J. (1997). The public health aspects of complex emergencies and refugee situations. *Annual Review of Public Health*, **18**, 283–312.
- VAN VUGT, M., BROCKMAN, A., GEMPERLI, B., LUXEMBURGER, C., GATHMANN, I., ROYCE, C., SLIGHT, T., LOOAREESUWAN, S., WHITE, N. J. & NOSTEN, F. (1998). Randomized comparison of artemether–benflumetol and artesunate–mefloquine in treatment of multidrug-resistant falciparum malaria. *Antimicrobial Agents and Chemotherapy*, **42**, 135–139.
- VAN VUGT, M., WILAIRATANA, P., GEMPERLI, B., GATHMANN, I., PHAIPUN, L., BROCKMAN, A., LUXEMBURGER, C., WHITE, N. J. & NOSTEN, F. (1999). Efficacy of six doses of artemether–benflumetol

in the treatment of multi-drug resistant falciparum malaria. *American Journal of Tropical Medicine and Hygiene*, **60**, 936–942.

WOLDAY, D. KIBREAB, T., BUKENYA, D. & HODES, R. (1995). Sensitivity of *Plasmodium falciparum* in vivo to chloroquine and pyrimethamine–sulfadoxine in Rwandan patients in a refugee camp in Zaire. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **89**, 654–656.

WORLD HEALTH ORGANIZATION (1999). *Outline Strategy for Malaria Control in Complex Emergencies*. Geneva: WHO.